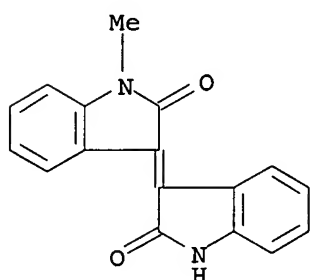


10/754547

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2006 ACS on STN
RN 97207-47-1 REGISTRY
ED Entered STN: 13 Jul 1985
CN 2H-Indol-2-one, 3-(1,2-dihydro-2-oxo-3H-indol-3-ylidene)-1,3-dihydro-1-methyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Dian III
CN Meisoindigo
CN N-Methylisoindigotin
MF C17 H12 N2 O2
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, CHEMCATS, MEDLINE, NAPRALERT, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

26 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
26 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file medicine

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COST IN U.S. DOLLARS

FULL ESTIMATED COST

SINCE FILE	TOTAL
ENTRY	SESSION
7.10	7.31

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FILE 'USPATFULL' ENTERED AT 14:50:21 ON 21 DEC 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 14:50:21 ON 21 DEC 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

=> s l1 or meisoinidigo
'CN' IS NOT A VALID FIELD CODE
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'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
L2 117 L1 OR MEISOINDIGO

=> s inflammation or anti inflammat?
14 FILES SEARCHED...
L3 2389166 INFLAMMATION OR ANTI INFLAMMAT?

=> s l3 and l4
L4 NOT FOUND

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10/754547

The L-number entered could not be found. To see the definition of L-numbers, enter DISPLAY HISTORY at an arrow prompt (=>).

=> s 12 and 13

29 FILES SEARCHED...

L4 15 L2 AND L3

=> dup rem

ENTER L# LIST OR (END):14

DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, DGENE, DRUGMONOG2, IMSPRODUCT, KOSMET, NUTRACEUT, PCTGEN, PHARMAML'.

ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE

PROCESSING COMPLETED FOR L4

L5 8 DUP REM L4 (7 DUPLICATES REMOVED)

=> d 15 1-8 ibib, kwic

L5 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2005:983776 CAPLUS

DOCUMENT NUMBER: 143:279380

TITLE: Methods using isoindigo, indigo, indirubin, and related compounds for treating an inflammatory-related disease

INVENTOR(S): Wang, Longgui; Liu, Xiao Mei; Mo, Lian; Mencher, Simon K.; McCarron, James P., Jr.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 40 pp., Cont.-in-part of U.S. Ser. No. 864,458.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005197381	A1	20050908	US 2005-104422	20050413
US 6566341	B1	20030520	US 2001-21589	20011213
WO 2003051900	A1	20030626	WO 2002-US39866	20021213
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
US 2005154046	A1	20050714	US 2004-754547	20040112
US 2004225002	A1	20041111	US 2004-864458	20040610
US 6933315	B2	20050823		

PRIORITY APPLN. INFO.:

US 2001-21589	A2	20011213
US 2002-407267P	P	20020903
WO 2002-US39866	A1	20021213
US 2004-754547	A2	20040112
US 2004-864458	A2	20040610

OTHER SOURCE(S): MARPAT 143:279380

AB The invention discloses pharmaceutical compns. and methods of treating

inflammatory-related diseases associated with proinflammatory cytokine expression and/or reduced expression of antiinflammatory cytokines. The method typically comprises administration of one or more compds. selected from isoindigo, indigo, indirubin, or derivs. thereof, e.g. Meisoindigo and NATURA. Preferably the pharmaceutical composition comprises one or more compds. selected from isoindigo, indigo, indirubin, or derivs. thereof, an antiinflammatory agent, and a pharmaceutically acceptable carrier.

- ST inflammation disease antiinflammatory isoindigo indigo indirubin; Meisoindigo Natura inflammation disease antiinflammatory
- IT Inflammation
(Crohn's disease; isoindigo, indigo, indirubin, and related compds. for treatment of inflammatory-related disease)
- IT Allergy
Eye, disease
Inflammation
(allergic conjunctivitis; isoindigo, indigo, indirubin, and related compds. for treatment of inflammatory-related disease)
- IT Allergy
Inflammation
Nose, disease
(allergic rhinitis; isoindigo, indigo, indirubin, and related compds. for treatment of inflammatory-related disease)
- IT Inflammation
Spinal column, disease
(ankylosing spondylitis; isoindigo, indigo, indirubin, and related compds. for treatment of inflammatory-related disease)
- IT Inflammation
Intestine, disease
(colitis; isoindigo, indigo, indirubin, and related compds. for treatment of inflammatory-related disease)
- IT Inflammation
Kidney, disease
(glomerulonephritis; isoindigo, indigo, indirubin, and related compds. for treatment of inflammatory-related disease)
- IT Inflammation
(granulomatous; isoindigo, indigo, indirubin, and related compds. for treatment of inflammatory-related disease)
- IT Allergy
Allergy inhibitors
Alzheimer's disease
Analgesics
Anemia (disease)
Anti-Alzheimer's agents
Anti-inflammatory agents
Antiarthritics
Antiasthmatics
Antidiabetic agents
Antidiarrheals
Antimalarials
Antiparkinsonian agents
Antirheumatic agents
Arthritis
Asthma
Atherosclerosis
Bone, disease
Cardiovascular agents
Cardiovascular system, disease

Celiac disease
 Combination chemotherapy
 Cystic fibrosis
 Dermatitis
 Diarrhea
 Digestive tract, disease
 Drug delivery systems
 Eye, disease
 Fibrosis
 Gastrointestinal agents
 Heart, disease
 Human
 Immunostimulants
 Immunosuppressants
 Inflammation
 Kidney, disease
 Leprosy
 Liver, disease
 Lung, disease
 Lupus erythematosus
 Metabolic disorders
 Multiple sclerosis
 Nervous system agents
 Parkinson's disease
 Psoriasis
 Rheumatoid arthritis
 Sarcoidosis
 Sjogren syndrome
 (isoindigo, indigo, indirubin, and related compds. for treatment of
 inflammatory-related disease)
 IT Inflammation
 Pancreas, disease
 (pancreatitis; isoindigo, indigo, indirubin, and related compds. for
 treatment of inflammatory-related disease)
 IT Biliary tract, disease
 Inflammation
 (sclerosing cholangitis; isoindigo, indigo, indirubin, and related
 compds. for treatment of inflammatory-related disease)
 IT Inflammation
 Intestine, disease
 (ulcerative colitis; isoindigo, indigo, indirubin, and related compds.
 for treatment of inflammatory-related disease)
 IT Eye, disease
 Inflammation
 (uveitis; isoindigo, indigo, indirubin, and related compds. for
 treatment of inflammatory-related disease)
 IT Blood vessel, disease
 Inflammation
 (vasculitis; isoindigo, indigo, indirubin, and related compds. for
 treatment of inflammatory-related disease)
 IT 50-02-2, Dexamethasone 50-23-7, Hydrocortisone 52-67-5, Penicillamine
 53-36-1, Methylprednisolone acetate 53-86-1, Indomethacin 76-25-5,
 Triamcinolone acetonide 89-57-6, Mesalamine 312-93-6, Dexamethasone
 phosphate 599-79-1, Sulfasalazine 1524-88-5, Flurandrenolide
 2152-44-5, Betamethasone valerate 3385-03-3, Flunisolide 6000-74-4,
 Hydrocortisone sodium phosphate 6054-98-4, Olsalazine sodium
 13609-67-1, Hydrocortisone butyrate 15687-27-1, Ibuprofen 22204-53-1,
 Naproxen 25122-46-7, Clobetasol propionate 38194-50-2, Sulindac
 51333-22-3, Budesonide 59865-13-3, Cyclosporine 64425-90-7, Choline

10/754547

magnesium trisalicylate 66734-13-2, Alclometasone dipropionate
69049-74-7, Nedocromil sodium 74103-07-4, Ketorolac tromethamine
77011-63-3, Beclomethasone dipropionate monohydrate 80474-14-2,
Fluticasone propionate 97207-47-1 141646-00-6, Mometasone
furoate monohydrate 162011-90-7, Rofecoxib 181695-72-7, Valdecocixib
213594-60-6, Balsalazide disodium 526194-76-3 864057-69-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(isoindigo, indigo, indirubin, and related compds. for treatment of
inflammatory-related disease)

L5 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2005:611844 CAPLUS
DOCUMENT NUMBER: 143:109788
TITLE: Methods of treating an inflammatory-related disease
INVENTOR(S): Wang, Longgui; Liu, Xiao Mei; Mo, Lian; Mencher, Simon
K.; McCarron, James P.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 37 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005154046	A1	20050714	US 2004-754547	20040112
CA 2547963	A1	20050804	CA 2005-2547963	20050106
WO 2005069933	A2	20050804	WO 2005-US169	20050106
WO 2005069933	A3	20050909		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
EP 1706112	A2	20061004	EP 2005-704992	20050106
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, BA, HR, IS, YU			
US 2005197381	A1	20050908	US 2005-104422	20050413
PRIORITY APPLN. INFO.:			US 2001-21589	A2 20011213
			US 2002-407267P	P 20020903
			WO 2002-US39866	A1 20021213
			US 2004-754547	A 20040112
			US 2004-864458	A2 20040610
			WO 2005-US169	W 20050106

OTHER SOURCE(S): MARPAT 143:109788
AB The invention relates to pharmaceutical compns. and methods of treating inflammatory-related diseases associated with pro-inflammatory cytokine expression and/or reduced expression of anti-inflammatory cytokines. The method typically comprises administration of one or more compds. selected from isoindigo, indigo,

indirubin, or derivs. thereof, such as, Meisoindigo and NATURA.
 Preferably the pharmaceutical composition comprises one or more compds.
 selected from isoindigo, indigo, indirubin, or derivs. thereof, an
 anti-inflammatory agent, and a pharmaceutically
 acceptable carrier.

- IT Inflammation
 (Crohn's disease; methods of treating inflammatory-related disease)
- IT Allergy
 Eye, disease
 Inflammation
 (allergic conjunctivitis; methods of treating inflammatory-related
 disease)
- IT Allergy
 Inflammation
 Nose, disease
 (allergic rhinitis; methods of treating inflammatory-related disease)
- IT Inflammation
 Spinal column, disease
 (ankylosing spondylitis; methods of treating inflammatory-related
 disease)
- IT Inflammation
 Intestine, disease
 (colitis, nonspecific; methods of treating inflammatory-related
 disease)
- IT Inflammation
 Kidney, disease
 (glomerulonephritis; methods of treating inflammatory-related disease)
- IT Inflammation
 (granulomatous; methods of treating inflammatory-related disease)
- IT Allergy
- Alzheimer's disease
- Analgesics
- Anemia (disease)
- Animals
- Anti-Alzheimer's agents
- Anti-inflammatory agents
- Antiarthritics
- Antiparkinsonian agents
- Antirheumatic agents
- Arthritis
- Asthma
- Atherosclerosis
- Bone, disease
- Cardiovascular system, disease
- Celiac disease
- Cystic fibrosis
- Dermatitis
- Diarrhea
- Digestive tract, disease
- Eye, disease
- Fibrosis
- Human
- Inflammation
- Kidney, disease
- Leprosy
- Liver, disease
- Lung, disease
- Lupus erythematosus
- Metabolic disorders

Multiple sclerosis
 Parkinson's disease
 Psoriasis
 Rheumatoid arthritis
 Sarcoidosis
 Sjogren syndrome
 (methods of treating inflammatory-related disease)
 IT Inflammation
 Pancreas, disease
 (pancreatitis; methods of treating inflammatory-related disease)
 IT Biliary tract, disease
 Inflammation
 (sclerosing cholangitis; methods of treating inflammatory-related disease)
 IT Inflammation
 Intestine, disease
 (ulcerative colitis; methods of treating inflammatory-related disease)
 IT Eye, disease
 Inflammation
 (uveitis; methods of treating inflammatory-related disease)
 IT Blood vessel, disease
 Inflammation
 (vasculitis; methods of treating inflammatory-related disease)
 IT 50-02-2, Dexamethasone 50-23-7, Hydrocortisone 52-67-5, Penicillamine 53-36-1, Methylprednisolone acetate 53-86-1, Indomethacin 77-86-1, Tromethamine 89-57-6, Mesalamine 124-94-7, Triamcinolone 312-93-6, Dexamethasone phosphate 476-34-6, Isoindigo 476-34-6D, Isoindigo, derivs. 479-41-4, Indirubin 479-41-4D, Indirubin, derivs. 482-89-3, Indigo 482-89-3D, Indigo, derivs. 599-79-1, Sulfasalazine 1524-88-5, Flurandrenolide 2152-44-5, Betamethasone valerate 3385-03-3, Flunisolide 4419-39-0, Beclomethasone 6000-74-4, Hydrocortisone sodium phosphate 13609-67-1, Hydrocortisone butyrate 15687-27-1, Ibuprofen 15722-48-2, Olsalazine 22204-53-1, Naproxen 25122-46-7, Clobetasol propionate 38194-50-2, Sulindac 51333-22-3, Budesonide 59865-13-3, Cyclosporin A 64425-90-7, Choline magnesium trisalicylate, biological studies 66734-13-2, Alclometasone dipropionate 69049-73-6, Nedocromil 74103-07-4, Ketorolac tromethamine 90566-53-3, Fluticasone 97207-47-1, Meisoindigo 141646-00-6, Mometasone furoate monohydrate 162011-90-7, Rofecoxib 181695-72-7, Valdecoxib 213594-60-6, Balsalazide Disodium 526194-76-3, Natura
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (methods of treating inflammatory-related disease)

L5 ANSWER 3 OF 8 USPATFULL on STN

DUPLICATE 3

ACCESSION NUMBER: 2004:286834 USPATFULL
 TITLE: Derivatives of isoindigo, indigo and indirubin and methods of treating cancer
 INVENTOR(S): Wang, Longgui, Flushing, NY, UNITED STATES
 Liu, Xiaomei, Flushing, NY, UNITED STATES
 Chen, Ruihuan, Foster City, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004225002	A1	20041111
	US 6933315	B2	20050823
APPLICATION INFO.:	US 2004-864458	A1	20040610 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. WO 2002-US39866, filed on 13 Dec 2002, PENDING Continuation of Ser. No. US		

2001-21589, filed on 13 Dec 2001, GRANTED, Pat. No. US
6566341

	NUMBER	DATE
	-----	-----
PRIORITY INFORMATION:	US 2002-407267P	20020903 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	WINSTON & STRAWN, PATENT DEPARTMENT, 1400 L STREET, N.W., WASHINGTON, DC, 20005-3502	
NUMBER OF CLAIMS:	17	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	13 Drawing Page(s)	
LINE COUNT:	1522	
CAS INDEXING IS AVAILABLE FOR THIS PATENT.		
SUMM	[0008] Our previous studies demonstrated that meisoindigo, a second generation of indirubins, arrests leukemia cells at G1 phase, inhibits expression of oncogene c-myc, and induces cell differentiation.	
SUMM	[0018] Additionally, the present invention provides a method of synthesizing a meisoindigo compound by adding about equal molar amounts of 2-hydroxyindole and N-methyl-indolinyldiketone to produce a reaction substance; mixing the reaction substance. . . about 70 to 80° C. for 1 to 3 hours to form a precipitate, and recovering the precipitate as the meisoindigo compound.	
DRWD	[0021] FIG. 1 shows the chemical structures of Indirubin, Meisoindigo, and NATURA, a new chemical entity in accordance with the invention.	
DRWD	. . . of DNA fragmentation in prostate cancer LNCaP cells (panel A) and neuroblastoma N2A cells (panel B) having been exposed to Meisoindigo, NATURA or Taxol.	
DRWD	[0032] FIG. 12. shows the effect of Meisoindigo and NATURA on the protein level of cyclin D1.	
DETD	[0053] Additionally, the present invention provides a method of synthesizing meisoindigo comprising: adding about equal molar amounts of 2-hydroxyindole and N-methyl-indolinyldiketone to produce a reaction substance; mixing the reaction substance with. . .	
DETD	[0078] Reagents: Meisoindigo and NATURA and other sugar derivatives were synthesized by Natrogen, purified by PHLC with a purity of 98.5%, and structures. . .	
DETD	. . . cell basal medium) and RPMI 1640 containing 10% FBS, respectively. The cells grown exponentially were exposed to indicated concentrations of meisoindigo or NATURA for 24 hr. The cells were harvested, washed, and total proteins extracted as described previously [13]. One hundred. . . (represent cdk activity) was measured by scintillation counting or by SDS-polyacrylamide gel electrophoresis [14, 15]. The direct inhibitory effects of Meisoindigo and NATURA were also measured by reaction of immuno-purified specific enzyme from untreated cells directly with the Meisoindigo or NATURA.	
DETD	. . . cancer cells including cancer cell lines of breast, prostate, colon and lung (IC ₅₀ are between 1.5 to 9.0 μM). Both Meisoindigo and NATURA also exhibit very low toxicity with LD ₅₀ in mice. The test data below is for Meisoindigo 3.9±0.8 g/kg, and for NATURA 7.33±1.15 g/kg as compared to a value for Cisplatin of 15.9±1.3 mg/kg under the same. . .	
DETD	. . . the targeting of those cancer cells that escape from treatments at the earlier stage of the cycle. At low concentrations, Meisoindigo inhibits cyclin-D mediated cdk activity, and at	

higher concentration, it interferes with both cyclin A and/or B mediated cdk activity.

DETD . . . cyclin A, cyclin B and cyclin E), the cyclin-dependent kinases (CDKs, cdk4/6, cdk2, and cdc2) and their inhibitors (p15/p16/p18/19, p21/p27). Meisoindigo and NATURA specifically inhibit activities of cdk4/6, cdk2, and cdc2, thus against cell proliferation. Those compounds have also showed to.

DETD [0086] Anticancer activity in animal models of Meisoindigo and NATURA: Two established animal cancer models, Lewis lung carcinoma, and Walker 256 sarcoma [17-20], have been used to evaluate anti-solid tumor activities of meisoindigo and NATURA as described previously. Briefly, C57 mice, body weight between 18 to 22 grams, and rat, body weight between. . . or Walker sarcoma cells were transplanted into mice or rat. Twenty-four hrs after the transplantation, equal molar dosages of indirubin, meisoindigo, NATURA or its sugar derivatives were given orally for 10 days. The animals in the control group were given 0.1.

DETD . . . of NATURA on Human Cancer Cells: A good response of different types of human cancer cells to the treatment of Meisoindigo and NATURA was obtained by MTT after three day exposure, including cancer cell lines of breast (MCF-7 and SKBR-3, Table. . . dependent and independent prostate (LNCaP, PC-3 and DU145, Table 3). As shown in Table 1-3, the growth inhibitory effects of Meisoindigo (IC₅₀ 2.15 to 8.31 μ M) on all of those tested human cancer cell lines are much stronger than retinoid acid. . . of NATURA (IC₅₀ from 1.64 to 6.92 μ M), the anticancer activities of NATURA is slightly stronger than its parental compound Meisoindigo (IC₅₀ 2.1 to 8.3 μ M). We expect that a much stronger anticancer activity of NATURA than Meisoindigo will occur in vivo due to a significant improvement of its bioavailability by increasing its solubility. Similar results for all. . . therapeutic agents, Casodex and Proscar (Table 3). No significant differences of those cancer cells in response to the treatment of Meisoindigo and NATURA were observed whereas cancer cells of breast and colon seem more sensitive than that of prostate (Table 3) in response to the treatment of Daunomycin. These data support that Meisoindigo and NATURA are against a common target of cancer cells, i.e. cyclin dependent kinases, thus it will be proven to. . . be a useful chemotherapeutic agent for the treatment of various types of human solid tumors. Although the anticancer effect of Meisoindigo and NATURA are weaker than that of daunomycin or paclitaxel in vitro assay, it is noted that the toxicities of Meisoindigo and NATURA may much lower than those of agents as implicated by their LD₅₀ (3.90 \pm 0.8 g/kg for Meisoindigo and 7.33 \pm 1.15 g/kg for NATURA in mice).

TABLE 1

Comparison of IC₅₀ (μ M) of Meisoindigo and NATURA with Chemotherapeutic Agents Against Breast Cancer Cell Lines by MTT

Agent	CELL LINE	
	MCF-7	SKBR-3
Meisoindigo	4.37 \pm 0.31	2.17 \pm 0.17
NATURA	2.91 \pm 0.28	1.71 \pm 0.14
Daunomycin	0.054 \pm 0.011	0.061 \pm 0.0051

DETD

TABLE 2

Comparison of IC₅₀ (μM) of NATURA with Chemotherapeutic Agents
Against Colon Cancer Cells by MTT

Agent	CELL LINE	
	LOVO	DLD-1
Meisoindigo	5.76 ± 0.72	2.15 ± 0.17
NATURA	4.31 ± 0.59	1.64 ± 0.181
Daunomycin	0.035 ± 0.004	0.094 ± 0.0130

DETD [0089]
TABLE 3

Comparison of IC₅₀ (μM) between Meisoindigo,
NATURA and Chemotherapeutic
Agents against Prostate Cancer Cell Lines.

Agent	CELL LINE		
	LNCaP	PC-3	DU145
Meisoindigo	2.34 ± 0.33	3.26 ± 0.51	8.31 ± 0.93
NATURA	1.72 ± 0.27	2.41 ± 0.39	6.92 ± 0.73
Daunomycin	N/A	0.24	

DETD . . . cell basal medium) and RPMI 1640 containing 10% FBS, respectively. The cells grown exponentially were exposed to indicated concentrations of meisoindigo or NATURA for 24 hr. The cells were harvested, washed, and total proteins extracted as described previously [13]. One hundred. . .

DETD [0092] The inhibitory nature of NATURA and Meisoindigo on Ckd4/6 activity is shown in FIG. 7. Two different concentrations of 5.0 and 15.0 μM were used. The lower. . .

DETD . . . enter apoptosis. Our studies have demonstrated that approximately 48% of ML-1 cells became differentiated morphologically 5 days after exposure to Meisoindigo or NATURA. We also observed some L1210 leukemia cells became apoptotic by flow cytometry (FCM), suggesting that Meisoindigo and NATURA have a capacity to induce cell apoptosis. FIG. 8 confirms that Meisoindigo and NATURA cause apoptosis. The formation of DNA fragmentation (ladder) were measured, an indicator of cell apoptosis, in both LNCaP. . . neuroblastoma cells. To do this LNCaP and neuroblastoma N2A cells at exponential growth phase were exposed to indicated concentrations of Meisoindigo or NATURA or Taxol (20 nM, as a positive control) for 2 days. The cells were harvested, washed and DNA. . . Approximately 2 μg per lane of DNA were subjected to 2% agarose gel electrophoresis. As shown in FIG. 8, both Meisoindigo and NATURA induced a significant DNA fragmentation in LNCaP cells at concentration of 15 μM. This action was found more potent in N2 A neuroblastoma than in LNCaP cells where 5 μM of either Meisoindigo or NATURA was sufficient to significantly induce DNA ladders (panel B) which was consistent with MTT data, indicating that N2 A neuroblastoma cells are more sensitive to either Meisoindigo or NATURA.

DETD Anticancer Activity of Meisoindigo In Vivo

DETD [0094] As shown in Table 4, Meisoindigo showed significant anticancer activities for both Lewis Lung cancer and Walker 256 sarcoma and the activities were much stronger than that of its parental compound indirubin.

TABLE 4

Anti-cancer activities of Meisoindigo and NATURA in animals.

Tumor	Statistic Group	Dose (mg/kgxd)	No. of animals	Tumor Size X \pm SD	Inhibition (%)	(ST.
	10	3.5 \pm 0.44	0			
Lung	Indirubin	100 + 9	10	2.58 \pm 0.21	26.3 \pm 2.8	
	P < 0.05					
Cancer	Meisoindigo	106 + 9	10	1.80 \pm 0.15		
	48.6 \pm 4.1	P < 0.01				
Walker	Control	--	10	9.7 \pm 1.02	0	
256	Indirubin	100 + 9	10	3.94 \pm 0.71	59.4 \pm 2.9	
	P < 0.01					
	Meisoindigo	106 + 9	10	2.10 \pm 0.17		
	71.6 \pm 3.1	P < 0.01				

DETD [0095] Previous studies have shown that Meisoindigo induces ML-1 cell differentiation and maturation while suppresses the expression of oncogene c-myc, and arrests the cancer cells at G1. . . kinase activity have been indicated to play a role induction of cell differentiation. In this preliminary observation, we further confirmed Meisoindigo strongly suppresses D cyclins mediated cdk4/6 activity (FIG. 2). Over 56% of the enzyme activity was inhibited by 5.0 μ M and complete inhibition was achieved when LNCaP prostate cancer cells were exposed to 15 μ M of Meisoindigo for 24 h. Similar results were also obtained in human epithelial cell line HUVEC cells (data not shown), indicating that Meisoindigo may also have anti-angiogenesis activity.

DETD [0096] These analyses indicate that Meisoindigo is an attractive therapeutic agent against various types of human cancers as they specifically target cyclin dependent kinases. Meisoindigo has already showed strong anticancer activities in animals. The stable and simple chemical structure of Meisoindigo makes it easy to synthesize and administer. Moreover, it possesses new chemical structure that exhibits anticancer activity, which can be. . .

DETD Chemical Synthesis of Meisoindigo. NATURA and its Derivatives:

DETD [0097] To synthesis Meisoindigo, typically, add equal molar amount of 2-hydroxyindole (see structure below) and N-methyl-indolinyldiketone, glacial acetic acid (2.0 L of glacial acetic. . .

DETD Synergistic Combinations of Meisoindigo:

DETD [0104] Effects of Meisoindigo in combinations with Casodex or Proscar or Casodex plus Proscar on prostate cancer cell growth were evaluated by MTT in. . . at density of 5,000 cells per well. Twenty-four hours after the incubation, the cells were exposed to series dilution of Meisoindigo, or Casodex or Proscar alone. For combinations, the cells were exposed to Meisoindigo with either Casodex or Proscar, or with Casodex plus Proscar at ratio of 1:10, 1:4 or 1:10:4, respectively. The maximal concentrations were 5 μ M for Meisoindigo, 50 μ M for Casodex, and 20 μ M for Proscar, respectively. Three days after the incubation, the cell growth was measured. . . combination. If CI>1, the combination is antagonistic, CI=1, additive, and CI<1, synergistic. As shown in Table 5-7, the combinations of Meisoindigo either with Casodex or Proscar or Casodex plus Proscar resulted in significant synergistic anti-proliferation effects as indicated by their combination index (CI).

TABLE 5

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Combination index (CI) of Meisoindigo and Casodex in LNCaP cells

Meisoindigo (μ M)	CASODEX (μ M)	Percent of Inhibition CI	
0.0098	0.0980	0.9580	0.454
0.0195	0.1950	0.8585	0.213
0.0390	0.3900	0.8000	0.275

DETD [0105]

TABLE 6

Combination index (CI) of Meisoindigo and Proscar in LNCaP cells

Meisoindigo (μ M)	Proscar (μ M)	Percent of Inhibition CI	
0.0195	0.0780	0.919	4.555
0.0390	0.1560	0.900	5.243
0.0780	0.3120	0.814	1.908

DETD [0106]

TABLE 7

Combination index (CI) of Meisoindigo and Casodex plus Proscar in LNCaP cells

Meisoindigo (μ M)	CASODEX (μ M)	Proscar (μ M)	Percent of Inhibition	CI
0.0098	0.0980	0.03904	0.8940	1.228
0.0195	0.1950	0.0780	0.8600	1.214
0.0390	0.3900	0.1560	0.7000	

DETD Toxicological Study of Meisoindigo

DETD . . . with body weight between 18-22 g were randomly divided into 8 groups each with 10 animals. The animals were given Meisoindigo suspension orally at dosage of 0, 1.85, 2.60, 3.60, 5.10, 7.14, and 10.00 g/kg respectively. The animals were tested for. . . with the highest dose. The data were shown in Table 8.

TABLE 8

Summary of frequency of death after administration of Meisoindigo.

Dose (g/kg)	Log Dose	DFP*	[DF].sup.2P.sup.2	Unit of DF
10.00	1.00	1.00	1.00	7.326
7.14	0.85	0.80	0.64	5.842
5.10	0.70	0.70	0.49	5.524

3.60. . .

DETD . . . rats with body weight between 60-70 g were randomly divided into 4 groups each with 10 animals, and orally given Meisoindigo daily at dosage of 0, 100, 200, and 400 mg/kg respectively for 30 days. Body weights of all tested animals. . . and kidney. A slight reduction of body weight increase was observed in the group of animals given 400 mg/kg of Meisoindigo. No differences between control and tested groups were observed in biochemical functions of blood, liver and kidney. Examination of histochemistry. . .

DETD [0116] Two dogs were initially tested for sub-acute toxicity of Meisoindigo. They were orally given 10 mg/kg daily for 3 months. Minor gastro intestinal irritations were observed occasionally. No

- biochemical changes. . . .
- DETD and vomiting as well as black-green stool. However, all of those symptoms disappeared after the termination of the treatment of Meisoindigo. Therefore, one dog was given an escalated dosage i.e., from 20 mg/kg to 40 mg/kg for additional 12 days after. . . . Histochemical examinations were performed in the dogs administered the highest dose, and showed cellular edema, fatty degeneration, and scatter hyperplasia inflammation in liver tissues.
- DETD [0119] On the basis of above initial tests, the sub-acute toxicities of Meisoindigo were further examined in dogs. Twelve dogs were randomly divided into 3 groups each having equal numbers of males and females, and orally given Meisoindigo at doses of 0, 5, and 10 mg/kg daily, respectively, for 6 months. No significant differences between control and tested. . . .
- DETD [0120] Twenty-four hours after the termination of Meisoindigo, half of the animal of each group were sacrificed, and dissected for pathological examination. No abnormalities were observed histochemically in. . . .
- DETD [0123] Meisoindigo at concentrations of 2, 20, 50, 100 and 200 µg/dish (10 cm), metabolically activated (+S9) and inactivated (-S9), were tested. . . . 2,7-2AF, and 2-hydroxy-anthraquinone were used as positive controls. No induction of reverse mutations were observed at all tested groups of Meisoindigo, metabolically activated or non-activated, whereas all groups of positive controls showed significant increases in reverse-mutated colony formation.
- DETD [0125] Ten KM white mice were divided into 5 groups, and given orally Meisoindigo at dosage of 0, 0.4, 0.8 and 2.0 g/kg (equal to 1/10, 1/5, and 1/10 of LD50, respectively) daily for. . . . polychromatic erythrocytes from bone marrow were stained with Giemsa to count micronuclei. No differences were obtained between negative control and Meisoindigo-tested groups (1.86, 1.33, and 2.66 per thousand for the tested groups compared with 1.33 per thousand of control group), whereas, . . . positive control (41.16 per thousand against negative control 1.33 per thousand). These data demonstrated a negative induction of micronuclei of Meisoindigo.
- DETD [0127] Human blood withdrawn from healthy males was cultured in the presence of metabolically activated, or non-activated different concentrations of Meisoindigo (0, 5, 10, and 25 µM) for 72 hrs, or aflatoxin B1 (AFB1) and mitomycin C (MMC) as positive controls. The aberration of chromosomes was then examined under microscope. No differences were found between negative controls and all Meisoindigo-tested groups, metabolically activated or non-activated, ($P > 0.05$), whereas, the differences between positive and negative controls were significant ($P < 0.01$).
- DETD [0128] Previous studies have shown that Meisoindigo induces ML-1 cell differentiation and maturation while suppresses the expression of oncogene c-myb, and arrests the cancer cells at G1. . . .
- DETD [0134] Our previous studies have showed that Meisoindigo induce ML-1 cell differentiation and maturation while suppressing the expression of oncogene c-myb, and arresting the cancer cells at G1. . . . its kinase activity have been shown to play a role in the induction of cell differentiation [25-27]. We further confirmed Meisoindigo strongly suppress D cyclins mediated cdk4/6 activity. Similar to Meisoindigo, after 24 hours incubation with LNCaP prostate cancer cells, NATURA at 5.0 µM and 15 µM inhibited cdk2 enzyme activity. . . . 4/6) from separated experiments was between 1.5 to 6.0 [M in LNCAP cells. No remarkable differences in the inhibitions of Meisoindigo and NATURA on those cdks were observed.

- DETD [0135] Similar results were also obtained in human epithelial cell line HUVEC cells (data not shown), indicating the Meisoindigo and NATURA may also have anti-angiogenesis activity.
- DETD [0136] The specificity of Meisoindigo and NATURA on cdk activities were further established by the examining the effects of those compounds on the activities of.
- DETD [0139] Meisoindigo and NATURA also significant inhibit expression of cyclin D1 in HUVEC cells. Exponentially growing HUVEC cells were exposed to 5.0 and 15 μ M of Meisoindigo and NATURA, 24 hrs after the exposures, the cells were harvested, washed, and total proteins extracted for Western blot analysis [13] using a monoclonal antibody specific against cyclin D1 (Dako). As shown in FIG. 12, both Meisoindigo and NATURA strongly inhibit expression of cyclin D1 in this cell lines. The cyclin D1 protein almost completely lost when the cells were exposed to 15 μ M of either Meisoindigo and NATURA. As a result, phosphorylation of a tumor suppressor protein Rb, a native substrate of cyclin D1 mediated cdks, . . .
- DETD . . . apoptosis. Our previous studies have demonstrated that approximately 48% of ML-1 cells became differentiated morphologically 5 days after exposure to Meisoindigo. We also observed some L1210 leukemia cells became apoptotic by flow cytometry (FCM), suggesting Meisoindigo also have a capacity to induce cell apoptosis. To confirm our hypothesis and earlier observations, we measured poly(ADP-ribose) polymerase (PARP). . . prostate and N2A neuroblastoma cells. LNCaP and neuroblastoma N2A cells at exponential growth phase were exposed to indicated concentrations of Meisoindigo or NATURA or Taxol (20 nM, as a positive control), for 2 days. The cells were harvested, washed and DNA. . . . Approximately 2 μ g per lane of DNA were subjected to 2% agarose gel electrophoresis. As shown in FIG. 8, both Meisoindigo and NATURA induced a significant DNA fragmentation in LNCaP cells at concentration of 15 μ M. This action was found more potent in N2 A neuroblastoma cells where 5 μ M of either Meisoindigo or NATURA was sufficient to significantly induce DNA ladders (panel B) which was consistent with MTT data, indicating that N2 A neuroblastoma cells are more sensitive to either Meisoindigo and NATURA.
- DETD . . . the DNA ladder formation, a strong induction of PARP protein degradation was observed when N2A cells were exposed to either Meisoindigo or NATURA (FIG. 13). Our data thus, demonstrate that both Meisoindigo and NATURA significantly induce human cancer cell apoptosis.
- DETD [0147] FIG. 12. shows the effect of Meisoindigo and NATURA on the protein level of cyclin D1. HUVEC cells grown exponentially were treated for 24 hrs with 5 and 15 mM of Meisoindigo and NATURA. The cells were harvested, washed, and total proteins extracted for Western blot analysis as previously described [1] using. . .
- DETD . . . shows the degradation of poly(ADP-ribose) polymerase in neuroblastoma N2A cells. N2A cells grown exponentially were treated with different concentrations of Meisoindigo or NATURA for 24 hours. The cells were harvested, washed, and total proteins extracted for determination of PARP degradation by. . .
- DETD [0158] 10. Ji, X. J., et al., Pharmacological studies of meisoindigo: absorption and mechanism of action. Biomed Environ Sci, 1991. 4(3): p. 332-7.
- DETD . . . of differentiation and down-regulation of c-myc gene expression in ML-1 human myeloblastic leukemia cells by the clinically effective anti-leukemia agent meisoindigo. Biochem Pharmacol, 1996. 51(11): p. 1545-51.

10/754547

CLM What is claimed is:
9. A method of synthesizing a meisoindigo compound comprising:
adding about equal molar amounts of 2-hydroxyindole and
N-methyl-indolinyldiketone to produce a reaction substance; mixing the
reaction substance. . . about 70 to 80° C. for 1 to 3 hours to
form a precipitate; and recovering the precipitate as the
meisoindigo compound.

IT 97207-47-1, Meisoindigo
(isoindigo, indigo, and indirubin derivs. for treatment of cancer, and
use with other agents)

L5 ANSWER 4 OF 8 NAPRALERT COPYRIGHT (C) 2006 BD. TRUSTEES, U. IL. on STN
ACCESSION NUMBER: 92:41131 NAPRALERT
DOCUMENT NUMBER: M08940
TITLE: STUDIES ON ANTINEOPLASTIC ACTION OF N-METHYLISOINDIGOTIN
AUTHOR: JI X J; ZHANG F R; LIU Y; GU Q M
CORPORATE SOURCE: INSTITUTE OF MATERIA MEDICA, CHINESE ACADEMY OF MEDICAL SCI,
BEIJING CHINA
SOURCE: YAO HSUEH HSUEH PAO (1985) 20 (4) p. 247-251.
DOCUMENT TYPE: (Research paper)
LANGUAGE: CHINESE
CHARACTER COUNT: 3104
ORGN .

ACTIVE

Comment(s): RESULTS SIGNIFICANT AT P < 0.05 LEVEL..

COMPOUND. Chemical name (CN): INDIGOTIN,ISO: N-METHYL

CAS Registry Number (RN): 97207-47-1

Class identifier (CI): INDOLE ALKALOID

TYPE OF STUDY (STY): IN VIVO Classification (CC): DNA SYNTHESIS
INHIBITION

Dosage Information: IP; RAT;. . . P < 0.01 LEVEL..

ANIMALS WERE DOSED TWICE.

COMPOUND. Chemical name (CN): INDIGOTIN,ISO: N-METHYL

CAS Registry Number (RN): 97207-47-1

Class identifier (CI): INDOLE ALKALOID

TYPE OF STUDY (STY): IN VIVO Classification (CC): DNA SYNTHESIS
INHIBITION

Dosage Information: GASTRIC INTUBATION;. . . P < 0.01 LEVEL..

ANIMALS WERE DOSED TWICE.

COMPOUND. Chemical name (CN): INDIGOTIN,ISO: N-METHYL

CAS Registry Number (RN): 97207-47-1

Class identifier (CI): INDOLE ALKALOID

TYPE OF STUDY (STY): IN VIVO Classification (CC): ANTITUMOR ACTIVITY

Dosage Information: GASTRIC INTUBATION; MOUSE;. . .

Qualitative results: INACTIVE

ILS

Comment(s): DOSING ON DAYS 1-8.

COMPOUND. Chemical name (CN): INDIGOTIN,ISO: N-METHYL

CAS Registry Number (RN): 97207-47-1

Class identifier (CI): INDOLE ALKALOID

TYPE OF STUDY (STY): IN VIVO Classification (CC): ANTITUMOR ACTIVITY

Dosage Information: GASTRIC INTUBATION; MOUSE;. . . AT P < 0.01

LEVEL.. DOSING ON DAYS 1-9..

COMPOUND. Chemical name (CN): INDIGOTIN,ISO: N-METHYL

CAS Registry Number (RN): 97207-47-1

Class identifier (CI): INDOLE ALKALOID

TYPE OF STUDY (STY): IN VIVO Classification (CC): ANTITUMOR ACTIVITY

Dosage Information: GASTRIC INTUBATION; MOUSE;. . . AT P < 0.01

LEVEL.. DOSING ON DAYS 1-9..
COMPOUND. Chemical name (CN): INDIGOTIN,ISO: N-METHYL
CAS Registry Number (RN): 97207-47-1
Class identifier (CI): INDOLE ALKALOID
TYPE OF STUDY (STY): IN VIVO Classification (CC): HEPATOTOXIC ACTIVITY
Dosage Information: GASTRIC INTUBATION; DOG;. . . 12 DAYS OF
DOSING AT 40 MG/KG. HISTOPATHOLOGICAL EXAMINATION OF THE
LIVER REVEALED CELL SWELLING, PARTIAL FATTY DEGENERATION,
AND FOCAL PROLIFERATIVE INFLAMMATION.
COMPOUND. Chemical name (CN): INDIGOTIN,ISO: N-METHYL
CAS Registry Number (RN): 97207-47-1
Class identifier (CI): INDOLE ALKALOID
TYPE OF STUDY (STY): IN VIVO Classification (CC): TOXIC EFFECT(GENERAL)
Dosage Information: GASTRIC INTUBATION; DOG;. . . OF THE LIVER
AFTER DOSING WITH 20 MG/KG FOR 73 DAYS REVEALED CELL
SWELLING, PARTIAL FATTY DEGENERATION, AND FOCAL
PROLIFERATIVE INFLAMMATION.
COMPOUND. Chemical name (CN): INDIGOTIN,ISO: N-METHYL
CAS Registry Number (RN): 97207-47-1
Class identifier (CI): INDOLE ALKALOID
TYPE OF STUDY (STY): IN VIVO Classification (CC): TOXICITY
ASSESSMENT(QUANTITATIVE)
Dosage Information: GASTRIC INTUBATION; MOUSE; LD50: 3.9 GM per KG
Qualitative results: .
COMPOUND. Chemical name (CN): INDIGOTIN,ISO: N-METHYL
CAS Registry Number (RN): ~~97207-47-1~~
Class identifier (CI): INDOLE ALKALOID

L5 ANSWER 5 OF 8 DGENE COPYRIGHT 2006 The Thomson Corp on STN

ACCESSION NUMBER: AEB26712 DNA DGENE

TITLE: Composition useful in the treatment of an
inflammatory-related disease such as arthritis comprises a
compound selected from isoindigo, indigo, indirubin or their
derivatives; anti-inflammatory agent and
carrier.

INVENTOR: Wang L; Liu X M; Mo L; Mencher S K; Mccarron J P

PATENT ASSIGNEE: (WANG-I)WANG L.

(LIUX-I) LIU X M.

(MOLL-I) MO L.

(MENC-I) MENCHER S K.

(MCCA-I) MCCARRON J P.

PATENT INFO: US 2005154046 A1 20050714

37

APPLICATION INFO: US 2004-754547 20040112

PRIORITY INFO: US 2004-754547 20040112

DOCUMENT TYPE: Patent

LANGUAGE: English

OTHER SOURCE: 2005-505477 [51]

DESCRIPTION: Human TNF-alpha gene amplifying RT-PCR primer, SEQ ID NO: 3.

TI. . . the treatment of an inflammatory-related disease such as arthritis
comprises a compound selected from isoindigo, indigo, indirubin or their
derivatives; anti-inflammatory agent and carrier.

KW Therapeutic; inflammation; antiinflammatory; immune disorder;
immunomodulator; autoimmune disease; immunosuppressive; metabolic
disorder; metabolic; bone disease; osteopathic; musculoskeletal disease;
cardiovascular disease; cardiovascular-gen.; liver disease;. . .

AB. . . invention relates to pharmaceutical compositions and methods for
treating inflammatory-related diseases associated with pro-inflammatory
cytokine expression and/or reduced expression of anti-
inflammatory cytokines. The composition comprises of a compound

selected from isoindigo, indigo, indirubin or their derivatives; an anti-inflammatory agent and a carrier. The invention is useful in the treatment of an inflammatory-related disease associated with cytokine expression levels. . . conjunctivitis; diabetic retinopathy; Sjogren's syndrome; uveitis; a pulmonary disorder such as allergic rhinitis, asthma, chronic obstructive pulmonary disease, chronic granulomatous inflammation, cystic fibrosis and sarcoidosis; a renal disease; dermatitis; HIV-related cachexia; cerebral malaria; ankylosing spondylitis; leprosy; anemia and fibromyalgia. The present . . . a real-time (RT)-PCR primer used for amplifying human tumor necrosis factor (TNF)-alpha gene. This sequence is used to illustrate that meisoindigo suppresses the secretion and expression of TNF-alpha in human monocytic cell line THP-1 cells.

L5 ANSWER 6 OF 8 DGENE COPYRIGHT 2006 The Thomson Corp on STN

ACCESSION NUMBER: AEB26710 DNA DGENE

TITLE: Composition useful in the treatment of an inflammatory-related disease such as arthritis comprises a compound selected from isoindigo, indigo, indirubin or their derivatives; anti-inflammatory agent and carrier.

INVENTOR: Wang L; Liu X M; Mo L; Mencher S K; Mccarron J P

PATENT ASSIGNEE: (WANG-I)WANG L.

(LIUX-I) LIU X M.

(MOLL-I) MO L.

(MENC-I) MENCHER S K.

(MCCA-I) MCCARRON J P.

PATENT INFO: US 2005154046 A1 20050714

APPLICATION INFO: US 2004-754547 20040112

PRIORITY INFO: US 2004-754547 20040112

DOCUMENT TYPE: Patent

LANGUAGE: English

OTHER SOURCE: 2005-505477 [51]

DESCRIPTION: Human IL-6 gene amplifying PCR primer, SEQ ID NO: 1.

TI. . . the treatment of an inflammatory-related disease such as arthritis comprises a compound selected from isoindigo, indigo, indirubin or their derivatives; anti-inflammatory agent and carrier.

KW Therapeutic; inflammation; antiinflammatory; immune disorder; immunomodulator; autoimmune disease; immunosuppressive; metabolic disorder; metabolic; bone disease; osteopathic; musculoskeletal disease; cardiovascular disease; cardiovascular-gen.; liver disease; . . .

AB. . . invention relates to pharmaceutical compositions and methods for treating inflammatory-related diseases associated with pro-inflammatory cytokine expression and/or reduced expression of anti-inflammatory cytokines. The composition comprises of a compound selected from isoindigo, indigo, indirubin or their derivatives; an anti-inflammatory agent and a carrier. The invention is useful in the treatment of an inflammatory-related disease associated with cytokine expression levels. . . conjunctivitis; diabetic retinopathy; Sjogren's syndrome; uveitis; a pulmonary disorder such as allergic rhinitis, asthma, chronic obstructive pulmonary disease, chronic granulomatous inflammation, cystic fibrosis and sarcoidosis; a renal disease; dermatitis; HIV-related cachexia; cerebral malaria; ankylosing spondylitis; leprosy; anemia and fibromyalgia. The present sequence is a gene-specific PCR primer used for amplifying human IL-6 gene. This sequence is used to illustrate that meisoindigo inhibits the secretion and expression of IL-6 in human monocytic cell line THP-1 cells.

10/754547

L5 ANSWER 7 OF 8 DGENE COPYRIGHT 2006 The Thomson Corp on STN

ACCESSION NUMBER: AEB26711 DNA DGENE

TITLE: Composition useful in the treatment of an inflammatory-related disease such as arthritis comprises a compound selected from isoindigo, indigo, indirubin or their derivatives; anti-inflammatory agent and carrier.

INVENTOR: Wang L; Liu X M; Mo L; Mencher S K; Mccarron J P

PATENT ASSIGNEE: (WANG-I)WANG L.

(LIUX-I) LIU X M.

(MOLL-I) MO L.

(MENC-I) MENCHER S K.

(MCCA-I) MCCARRON J P.

PATENT INFO: US 2005154046 A1 20050714 37

APPLICATION INFO: US 2004-754547 20040112

PRIORITY INFO: US 2004-754547 20040112

DOCUMENT TYPE: Patent

LANGUAGE: English

OTHER SOURCE: 2005-505477 [51]

DESCRIPTION: Human IL-6 gene amplifying PCR primer, SEQ ID NO: 2.

TI. . . the treatment of an inflammatory-related disease such as arthritis comprises a compound selected from isoindigo, indigo, indirubin or their derivatives; anti-inflammatory agent and carrier.

KW Therapeutic; inflammation; antiinflammatory; immune disorder; immunomodulator; autoimmune disease; immunosuppressive; metabolic disorder; metabolic; bone disease; osteopathic; musculoskeletal disease; cardiovascular disease; cardiovascular-gen.; liver disease; . . .

AB. . . invention relates to pharmaceutical compositions and methods for treating inflammatory-related diseases associated with pro-inflammatory cytokine expression and/or reduced expression of anti-inflammatory cytokines. The composition comprises of a compound selected from isoindigo, indigo, indirubin or their derivatives; an anti-inflammatory agent and a carrier. The invention is useful in the treatment of an inflammatory-related disease associated with cytokine expression levels. . . conjunctivitis; diabetic retinopathy; Sjogren's syndrome; uveitis; a pulmonary disorder such as allergic rhinitis, asthma, chronic obstructive pulmonary disease, chronic granulomatous inflammation, cystic fibrosis and sarcoidosis; a renal disease; dermatitis; HIV-related cachexia; cerebral malaria; ankylosing spondylitis; leprosy; anemia and fibromyalgia. The present sequence is a gene-specific PCR primer used for amplifying human IL-6 gene. This sequence is used to illustrate that isoindigo inhibits the secretion and expression of IL-6 in human monocytic cell line THP-1 cells..

L5 ANSWER 8 OF 8 DGENE COPYRIGHT 2006 The Thomson Corp on STN

ACCESSION NUMBER: AEB26713 DNA DGENE

TITLE: Composition useful in the treatment of an inflammatory-related disease such as arthritis comprises a compound selected from isoindigo, indigo, indirubin or their derivatives; anti-inflammatory agent and carrier.

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DESCRIPTION: Human TNF-alpha gene amplifying PCR primer, SEQ ID NO: 4.

TI. . . the treatment of an inflammatory-related disease such as arthritis comprises a compound selected from isoindigo, indigo, indirubin or their derivatives; anti-inflammatory agent and carrier.

KW Therapeutic; inflammation; antiinflammatory; immune disorder; immunomodulator; autoimmune disease; immunosuppressive; metabolic disorder; metabolic; bone disease; osteopathic; musculoskeletal disease; cardiovascular disease; cardiovascular-gen.; liver disease; . . .

AB. . . invention relates to pharmaceutical compositions and methods for treating inflammatory-related diseases associated with pro-inflammatory cytokine expression and/or reduced expression of anti-inflammatory cytokines. The composition comprises of a compound selected from isoindigo, indigo, indirubin or their derivatives; an anti-inflammatory agent and a carrier. The invention is useful in the treatment of an inflammatory-related disease associated with cytokine expression levels. . . conjunctivitis; diabetic retinopathy; Sjogren's syndrome; uveitis; a pulmonary disorder such as allergic rihinitis, asthma, chronic obstructive pulmonary disease, chronic granulomatous inflammation, cystic fibrosis and sarcoidosis; a renal disease; dermatitis; HIV-related cachexia; cerebral malaria; ankylosing spondylitis; leprosy; anemia and fibromyalgia. The present. . . is a RT-PCR primer used for amplifying human tumor necrosis factor (TNF)-alpha gene. This sequence is used to illustrate the meisoindigo suppresses the secretion and expression of TNF-alpha in human monocytic cell line THP-1 cells.